Research Article

Evaluating the effectiveness of antidepressant therapy adjuvant to gabapentin and pregabalin for treatment of SCI-related neuropathic pain

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Objective: To investigate if a combination of anticonvulsant and antidepressant, two primary therapies for neuropathic pain, is associated with improved pain control compared to individual therapy.
Design: Prospective cohort study
Setting: The University of Alabama at Birmingham Rehabilitation Center In-patient Program between 2012 and 2015.
Participants: Incident SCI cases, 19–65 years of age.
Outcomes: Bryce-Ragnarsson pain classification scheme and the Numerical Rating Scale
Results: Twenty-nine eligible patients completed 6-month follow-up; their average age was 36.4 years, 89% were male, and 65% were white. Baseline characteristics were not different by therapy initiated (combination versus single). At 6 months follow-up, therapy initiated at baseline was not associated with level of pain in the past week ($p = 0.3145$) or past 24 hours ($p = 0.4107$). However, patients who remained on the same therapy reported lower levels of pain 30 minutes after waking ($p = 0.0235$).
Conclusions: The initiation of a combination of anticonvulsant and antidepressant shortly after SCI was not associated with improved pain control at 6 months compared to individual therapy. Adherent patients reported lower levels of pain; further analysis is warranted to elucidate this association.

Keywords: Anticonvulsant, Antidepressant, Neuropathic pain, Pain management, Spinal cord injury

Introduction

Annually, the number of incident cases of spinal cord injuries (SCI) in the US who do not die at the scene is around 12,500.[1] Between 65 and 85% of those with SCI experience chronic pain. Of those reporting pain, as many as 50% report the pain as being severe and 83% have more than one pain problem.[2,3]

The International Association for the Study of Pain (IASP) and the International Spinal Cord Injury Basic Pain Data Set (ISCIBPDS) defined three types of pain associated with SCI: musculoskeletal (MSK), neuropathic (NP), and visceral.[4–6] Visceral pain tends to be rare in individuals within the first year of SCI[3,7] and will not be covered in this paper.

MSK pain occurs in the musculoskeletal structures and often occurs above the level of injury. Pharmacologically it responds to nonsteroidal anti-inflammatory drugs (NSAIDs) or opioids.[5,6] NP pain is relatively common and the prevalence is estimated between 60 and 70% of people with SCI have NP pain.[8] Different approaches for classifying and quantifying this type of pain have been applied to examine SCI-related pain and the underlying mechanisms remain poorly understood.[3,5,6,8] In general therapies for NP pain from SCI are derived from other diseases and populations, such as therapies used to treat diabetic neuropathy, phantom limb pain, or trigeminal neuralgia,[6,8,9] with anticonvulsants and antidepressants being the primary therapies.[8,10] However, they may not always be as effective for NP pain of SCI origin, as suggested by previous studies.[2,5,8,9,11]

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Tricyclic antidepressants (TCAs) were considered the primary method of treating NP pain for more than 30 years.[8] Trials which have examined the efficacy of using antidepressants of any class to treat pain have had mixed results.[2,5,6,12–15] However, there have been reports that a combination of anticonvulsants and tricyclic antidepressants is more effective than either medication alone.[6] Selective Serotonin Reuptake Inhibitors (SSRI) and the newer Serotonin-Norepinephrine Reuptake Inhibitors (SNRI) have fewer adverse side effects and are usually tolerated better than TCAs.[8] Some studies have indicated that MSK pain may respond to TCAs and SNRIs; however, the effect on SSRIs have been more mixed.[16–18] Because MSK is so prevalent in patients with SCI and may respond to similar treatments, MSK pain was examined in the current analysis.

Researchers have discovered that a prime feature of NP pain is neuronal excitability similar to epilepsy.[10,19–21] It is believed that gabapentin and pregabalin act on NP pain by reducing central sensitization.[22] Some studies of anticonvulsants report that gabapentin and pregabalin may greatly reduce NP pain in individuals with SCI.[9,22] Placebo controlled drug trials have indicated that doses of gabapentin at up to 3,600 mg/day in divided doses significantly reduced pain and improved mood, sleep, and quality of life.[8] Gabapentin is currently considered a first line treatment for chronic, long-term at- and below-level NP pain.[6]

While opioids have a long history of improving MSK pain in many diseases and conditions, the results are less consistent with NP pain.[5,8,9] Some patients do appear to experience at least partial relief if a sufficient dose is used, when combined with anticonvulsants good results may be achieved by using lower doses of each drug (anticonvulsant and opioid).[5,8]

Because the first choices of treatment for SCI-related NP pain are anticonvulsants like gabapentin and pregabalin and second line of defense includes antidepressants, this study will focus on both of these medications. The aims of this study are to determine if medication therapy with an anticonvulsant and an antidepressant is related to self-reported pain ratings at baseline and 6-month follow-up assessments (Cross-sectional) and determine if medication therapy with an anticonvulsant and an antidepressant at baseline is related to self-reported pain ratings at follow-up (Longitudinal).

Methods

Participants

The subjects of the present study were patients admitted to the University of Alabama at Birmingham (UAB) Spain Rehabilitation Center (SRC) Inpatient Rehabilitation Program between January 2012 and September 2015. Eligible participants were required to be between 19 and 65 years of age and had suffered a traumatic SCI. Participants were excluded if their SCI was of non-traumatic origin, if they were non-English speakers, and/or had a history of moderate to severe traumatic brain injury. Of the 99 individuals who were approached to participate, sixty-four individuals consented and were enrolled in the study. No difference in age, gender, or race was found between those who declined to participate in the study and those who consented to participate in the study. Written consent was obtained from all subjects in the presence of a witness. The study protocol was approved and monitored by the UAB Institutional Review Board.

Study design

This was a prospective follow-up study. Participants were assessed at their admission to the inpatient rehabilitation program at SRC, which was defined as the baseline visit. Admission to SRC generally occurs two to four weeks after injury, but this timeline may vary depending on the extent of injury. The follow-up phone assessment occurred approximately 6 months after the date of injury.

Measures

Demographic and injury profile

Demographic characteristics were obtained through structured interview with the participants or from medical records. Neurological examinations to determine the patient's level of sensation, motor innervation, and American Spinal Injury Association (ASIA) Impairment rating were performed by physicians and were abstracted from the medical record.

Pain classification

The IASP/ISCIBPDS pain assessment recommendations were followed for this study and up to 3 worst pain sites were identified and assessed for each participant using the Bryce-Ragnarsson pain classification scheme.[4] Pain sites were classified by type of pain (MSK, NP, Mixed Pain, or Visceral Pain) and location of pain (Above level, At level, Below level, and At and Below level). At follow-up, participants stated any changes to occurrence of pain at these sites.

Pain rating

The pain sites assessed for each individual were rated using the Numerical Rating Scale (NRS). The NRS is an 11 point scale ranging from 0 which means "No Pain" to 10 "The worse pain imaginable."[23] For this study, participants were asked to rate their pain based on the average intensity for the past week, the past 24 hours, and their current level of pain at baseline and follow-up.

Depression

The Patient Health Questionnaire (PHQ-9)[24] depression scale is based on the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition criteria for major depressive disorder. Participants rated the nine items on a 4-point scale which ranges from "0 – Not at all" to "3- Nearly every day" to determine how often they experienced the symptoms in the past 2 weeks. PHQ-9 total scores may be classified as mild (scores between 5 and 9), moderate (scores between 10 and 14), moderately severe (scores between 15 and 19), or severe depression (scores of 20 or higher). Participants answered this questionnaire at baseline and follow-up.

Medication

Medications prescribed at baseline and 6-month follow-up were obtained from medical records. During the 6-month follow-up call the list of medications was reviewed with the participant for accuracy and to verify that the participant was continuing to take the medications their physician had prescribed. Medications of interest and ascertained in this study included anticonvulsants (gabapentin and pregabalin), antidepressants (SSRIs and SNRIs), and opioids. Patients who were exposed to anticonvulsant or antidepressant therapies prior to or at the time of SCI per self-report or medical record review were excluded from the study. Since opioids have been shown to be effective in the management of chronic pain generally and in some cases NP pain, the morphine equivalent dose (MED) was also accounted for and used as a covariate. MED is a method of standardizing opioid dose in order to compare the strength of each medication.[25,26] The opioid dose calculator developed by the Washington State Agency Medical Director's Group found at http://www.agencymeddirectors.wa.gov/Calculator/DoseCalculator.htm was used for each calculation. Participants were categorized into 3 groups based on their exposure at baseline as follows: 1) Combination therapy (anticonvulsant and antidepressant), 2) single therapy (anticonvulsant or antidepressant only), and 3) none (had neither therapy).

Data analysis

Descriptive statistics were calculated to examine whether there are any differences in the distributions of demographic, clinical, and SCI-related patient characteristics by the study participants' medication exposure at baseline. Fisher's Exact tests and ANOVAs were used to assess whether any observed difference is statistically significant.

The unit of analysis for the regression models is pain site. Since participants may experience multiple pain sites, pain therefore represents multiple observations nested within each individual and are not independent.[7] To address this issue, a general linear mixed model was used to examine the association between pain medication use and level of pain. For level of pain, we considered pain types for the NRS ratings obtained at baseline and at 6-month follow-up: average pain in the past week, average pain in the past 24 hours, average pain 30 minutes after waking up, and pain at time of assessment. Covariates controlled for in the model included age, race, time since injury, level and completeness of injury, PHQ-9 total score, and morphine equivalent dose amounts. For the models assessing NRS rating at 6 months follow-up, pain at the baseline assessment as well as a covariate indicating if they were on the same therapy as at the baseline assessment were also

Table 1 Demographics of sample followed and not followed.

	Followed (n=29)	Not Followed (n=31)	p-value
Age	36.4 (13.4)	33.8 (12.3)	0.4397
Gender			0.3022
Male	26 (89.7%)	24 (77.4%)	
Female	3 (10.3%)	7 (22.6%)	
Race			0.4296
White	19 (65.5%)	16 (53.3%)	
Non-White	10 (34.5%)	14 (46.7%)	
Education	12.3 (1.6)	11.8 (2.7)	0.3634
Marital Status			0.3117
Never Married	11 (37.9%)	18 (58.1%)	
Married	13 (44.8%)	10 (32.3%)	
Divorced	5 (17.2%)	3 (9.7%)	
Etiology of Injury			0.9209
Fall	4 (13.8%)	4 (13.3%)	
Vehicular	16 (55.2%)	19 (63.3%)	
Violence	7 (24.1%)	5 (16.7%)	
Other	2 (6.9%)	2 (6.7%)	
SCI Level of Injury			0.0322
Cervical	8 (27.6%)	17 (54.8%)	
Thoracic	18 (62.1%)	14 (45.2%)	
Lumbar	3 (10.3%)	0	
Pain Type			0.3087
MSK	19 (65.5%)	14 (46.7%)	
NP	7 (24.1%)	9 (30.0%)	
Mixed	3 (10.3%)	7 (23.3%)	
ASIA Severity			0.6835
A	19 (65.5%)	19 (61.3%)	
B	2 (6.9%)	4 (12.9%)	
C	3 (10.3%)	5 (16.1%)	
D	5 (17.2%)	3 (9.7%)	
Days since Injury	32.3 (17.2)	29.8 (13.7)	0.5747
Baseline PHQ-9	7.2 (6.0)	7.7 (5.8)	0.7321
Number of pain sites	2.5 (1.2)	2.9 (1.3)	0.1814
MED	117.8 (64.0)	112.4 (81.1)	0.7749

Note: Values are n (%), mean ± SD.
p-values calculated with Fisher's exact or ANOVA.

included in the models.. All analyses were conducted using SAS v.9.4 (SAS Institute Inc, Cary, NC).

Results

Of the sixty-four participants recruited to the study, four were excluded from analysis. Two participants were excluded due to incompleteness of data. Two other participants were excluded due to use of antidepressants at the time of their injury as assessed through medical record review and participant self-report. Twenty-nine participants completed 6-month follow-up assessments. There was a significant difference between those who completed follow-up and those who did not complete follow up for SCI level of injury ($p=0.0322$). There were no other significant differences between participants who did and did not complete the follow-up assessments for demographic, clinical, and SCI-related patient characteristics. Table 1 details demographic and injury related characteristics comparing the individuals who completed follow-up to those who did not.

For the 60 individuals included in this analysis, participants had an average age of 35, were predominantly male (83.3 %) and most were white (59.3%). The primary cause of injury was vehicular (59.3%) and most sustained a thoracic level injury (53.3%) with an ASIA rating of A (complete injury- 63.3%). The average time between injury and baseline assessment was approximately 31 days with a range of 8 to 89 days. This was related to the extent of injury and additional medical complications sustained at the time of SCI. Individuals with a more severe injury had a corresponding longer time between injury and baseline assessment. Participants receiving combination therapy versus single therapy did not differ with regard to their demographic and injury related characteristics. Detailed information is presented in Table 2.

At baseline there were 140 pain sites with an average of 2.7 per person. Of these pain sites, 43 were neuropathic, 75 were musculoskeletal, and 18 were mixed. Four pain sites were not classified by pain type and were not included in analysis by pain type.

NRS ratings at baseline and follow-up

Factors cross-sectionally associated with baseline pain level from mixed models

Individuals who had neither therapy had lower average pain ratings in the last week, in the last 24 hours, 30

Table 2 Demographics of sample at baseline.

	All Sample (n=60)	None (n=10)	Single Therapy (n=38)	Combination Therapy (n=12)	p-value
Age	35.1 (12.8)	34.7 (13.9)	35.4 (12.2)	34.4 (14.5)	0.9694
Gender					0.8895
Male	50 (83.3%)	8 (80.0%)	32 (84.2%)	10 (83.3%)	
Female	10 (16.7%)	2 (20.0%)	6 (15.8%)	2 (16.7%)	
Race					0.9280
White	35 (59.3%)	6 (60.0%)	21 (56.8%)	8 (66.7%)	
Non-White	24 (40.7%)	4 (40.0%)	16 (43.2%)	4 (33.3%)	
Education	12.0 (2.3)	12.4 (2.0)	12.1 (2.3)	11.6 (2.4)	0.6934
Marital Status					0.6931
Never Married	29 (48.3%)	5 (50.0%)	17 (44.7%)	7 (58.3%)	
Married	23 (38.3%)	3 (30.0 %)	17 (44.7%)	3 (25.0%)	
Divorced	8 (13.3%)	2 (20.0%)	4 (10.5%)	2 (16.7%)	
Etiology of Injury					0.8474
Fall	8 (13.6%)	1 (10.0%)	5 (13.5%)	2 (16.7%)	
Vehicular	35 (59.3%)	5 (50.0%)	24 (64.9%)	6 (50.0%)	
Violence	12 (20.3%)	3 (30.0%)	6 (16.2%)	3 (25.0%)	
Other	4 (6.8%)	1 (10.0%)	2 (5.4%)	1 (8.3%)	
SCI Level of Injury					0.4720
Cervical	25 (41.7%)	3 (30.0%)	15 (39.5%)	7 (58.3%)	
Thoracic	32 (53.3%)	7 (70.0%)	21 (55.3%)	4 (33.3%)	
Lumbar	3 (5.0%)	0	2 (5.3%)	1 (8.3%)	
ASIA Severity					0.3442
A	38 (63.3%)	7 (70.0%)	24 (63.2%)	7 (58.3%)	
B	6 (10.0%)	0	3 (7.9%)	3 (25.0%)	
C	8 (13.3%)	2 (20.0%)	4 (10.5%)	2 (16.7%)	
D	8 (13.3%)	1 (10.0%)	7 (18.4%)	0	
Days since Injury	30.9 (15.4)	31.4 (19.1)	28.7 (12.1)	37.3 (20.5)	0.2394
Baseline PHQ-9	7.5 (5.8)	4.6 (3.5)	7.8 (5.5)	9.0 (7.7)	0.1903
Number of pain sites	2.7 (1.3)	2.6 (1.1)	2.9 (1.4)	2.2 (0.8)	0.1913
MED	115.0 (72.7)	116.5 (54.5)	109.6 (68.1)	131.0 (99.8)	0.6798

Note: Values are n (%), mean ± SD.
p-values calculated with Fisher's exact or ANOVA.

minutes after awakening, and at the time of assessment compared to those on one treatment only or both (respective $P = 0.0017$, 0.0014, 0.0515, 0.0048). Other patient characteristics associated with having lower pain ratings in the last week, last 24 hours, and at the time of assessment included Caucasian (respective $P = 0.0077$, 0.0252, 0.0138) and musculoskeletal pain type (respective $P = 0.0299$, 0.0455, 0.0195). Pain sites classified as being musculoskeletal were generally given lower pain ratings that mixed or NP pain sites. Higher morphine equivalent dose was also associated with lower reported pain at the time of assessment ($P = 0.0459$). Further results of this analysis appear in Table 3.

Table 3 Significant patient characteristics at baseline assessment.

	LS Means or PE	P-value
Average pain in the last week		
Therapy group- Neither	4.77	0.0017
Therapy group- One	6.60	0.2500
Therapy group- Both	7.41	*ref*
White	5.99	*ref*
Non-White	7.24	0.0077
Pain Type- MSK	6.08	0.0299
Pain Type- NP	7.03	*ref*
Pain Type- Mixed	6.88	0.6999
MED (per 100 unit increase)	0.01	0.9788
Average pain in the last 24 hours		
Therapy group- Neither	4.01	0.0014
Therapy group- One	6.15	0.2669
Therapy group- Both	6.95	*ref*
White	5.58	*ref*
Non-White	6.60	0.0252
Pain Type- MSK	5.59	0.0455
Pain Type- NP	6.53	*ref*
Pain Type- Mixed	6.32	0.8149
MED (per 100 unit increase)	0.46	0.2278
Pain 30 minutes after waking		
Therapy group- Neither	3.73	0.0515
Therapy group- One	5.43	0.4732
Therapy group- Both	5.87	*ref*
White	4.70	*ref*
Non-White	6.10	0.0571
Pain Type- MSK	5.31	0.8288
Pain Type- NP	5.26	*ref*
Pain Type- Mixed	5.06	0.8789
MED (per 100 unit increase)	0.56	0.3216
Pain at time of assessment		
Therapy group- Neither	2.71	0.0048
Therapy group- One	4.55	0.0590
Therapy group- Both	6.05	*ref*
White	4.19	*ref*
Non-White	5.15	0.0138
Pain Type- MSK	3.97	0.0195
Pain Type- NP	5.41	*ref*
Pain Type- Mixed	5.05	0.6569
MED (per 100 unit increase)	0.86	0.0459

Parameter estimates are presented for continuous variables; Least squares means are presented for categorical variables.

Factors cross-sectionally associated with pain ratings at 6 month follow-up

Treatment group was not found to be significantly associated with NRS pain ratings in the past week, past 24 hours, 30 minutes after waking, and at the time of follow-up assessment. Higher PHQ-9 total score was significantly associated with higher pain scores in the last week, last 24 hours, and 30 minutes after awakening (respective $P = 0.0351$, 0.0246, 0.0157). Further results of this analysis appear in Table 4.

Factors longitudinally associated with pain ratings at 6 month follow-up

Individuals classified as having single therapy at baseline reported higher levels of pain 30 minutes after awakening at the time of follow-up assessment compared to individuals on combination therapy (P= 0.0418). Treatment was not significantly associated with NRS pain ratings in the past week, past 24 hours, and at the time of follow-up assessment; however, individuals who remained on the same therapy reported significantly lower levels of pain over the past 24 hours leading to their follow-up and 30 minutes after waking up on the day of follow-up (respective $P = 0.0489$, 0.0235) than did individuals who stopped taking the medications prescribed at baseline. Individuals who changed therapy group (as detailed in Table 5) were those who did not remain in the same therapy group (None, Single, or Combination) at follow-up. Of the

Table 4 Significant patient characteristics at follow-up assessment.

	LS Means or PE	P-value
Average pain in the last week		
Therapy group- Neither	2.36	0.6255
Therapy group- One	3.03	0.4743
Therapy group- Both	3.25	*ref*
PHQ-9 Total Score	0.22	0.0351
Average pain in the last 24 hours		
Therapy group- Neither	2.02	0.7517
Therapy group- One	2.70	0.6501
Therapy group- Both	3.34	*ref*
PHQ-9 Total Score	0.24	0.0246
Pain 30 minutes after waking		
Therapy group- Neither	2.90	0.2919
Therapy group- One	3.06	0.3309
Therapy group- Both	3.11	*ref*
PHQ-9 Total Score	0.31	0.0157
Pain at time of assessment		
Therapy group- Neither	1.36	0.9833
Therapy group- One	2.46	0.6220
Therapy group- Both	2.90	*ref*
PHQ-9 Total Score	0.18	0.0651

Parameter estimates are presented for continuous variables; Least squares means are presented for categorical variables.

Table 5 Significant patient characteristics at follow-up assessment associated with baseline treatment.

	LS Means or PE	P-value
Average pain in the last week		
Therapy group- Neither	1.78	0.5333
Therapy group- One	2.92	0.3145
Therapy group- Both	3.56	*ref*
Maintained Therapy Group	2.66	*ref*
Changed Therapy Group	3.04	*0.0559*
White	2.95	*ref*
Non-White	2.48	0.1221
PHQ-9 Total Score	0.22	0.0563
Injury Class- Complete Paraplegia	2.16	*0.5464*
Injury Class- Complete Tetraplegia	3.25	0.1984
Injury Class- Incomplete Paraplegia	3.08	0.2515
Injury Class- Incomplete Tetraplegia	4.04	*ref*
Average pain in the last 24 hours		
Therapy group- Neither	1.11	0.9729
Therapy group- One	2.67	0.4107
Therapy group- Both	3.70	*ref*
Maintained Therapy Group	2.53	*ref*
Changed Therapy Group	2.55	*0.0489*
White	2.76	*ref*
Non-White	2.02	0.0630
PHQ-9 Total Score	0.21	0.0541
Injury Class- Complete Paraplegia	1.89	0.7040
Injury Class- Complete Tetraplegia	3.25	*0.1147*
Injury Class- Incomplete Paraplegia	2.52	0.1252
Injury Class- Incomplete Tetraplegia	3.93	*ref*
Pain 30 minutes after waking		
Therapy group- Neither	1.53	0.2504
Therapy group- One	3.22	0.0418
Therapy group- Both	3.29	*ref*
Maintained Therapy Group	2.87	*ref*
Changed Therapy Group	2.99	0.0235
White	3.25	*ref*
Non-White	2.14	0.0078
PHQ-9 Total Score	0.33	0.0096
Injury Class- Complete Paraplegia	2.12	0.3568
Injury Class- Complete Tetraplegia	3.50	0.0552
Injury Class- Incomplete Paraplegia	2.91	0.0534
Injury Class- Incomplete Tetraplegia	4.70	*ref*
Pain at time of assessment		
Therapy group- Neither	0.94	0.8621
Therapy group- One	2.32	0.4029
Therapy group- Both	3.04	*ref*
Maintained Therapy Group	2.23	*ref*
Changed Therapy Group	2.09	0.0750
White	2.29	*ref*
Non-White	1.89	0.1475
PHQ-9 Total Score	0.15	0.1235
Injury Class- Complete Paraplegia	1.37	0.4098
Injury Class- Complete Tetraplegia	3.00	0.1661
Injury Class- Incomplete Paraplegia	2.60	0.2162
Injury Class- Incomplete Tetraplegia	3.54	*ref*

Parameter estimates are presented for continuous variables; Least squares means are presented for categorical variables.

29 subjects who were followed, 17 remained in the same therapy group 6 months after their initial injury. An additional factor associated with lower pain scores in the past 24 hours and 30 minutes after waking up was a lower PHQ-9 Total Score at the time of assessment (respective $P=$ 0.0541, 0.0096). Additionally, Caucasians reported lower pain 30 minutes after awakening ($P=$ 0.0078). Table 5 displays detailed summary statistics.

Discussion

Current guidelines that exist are derived from anecdotal evidence or underpowered, poorly designed clinical trials.[8] Some of the more recent systematic reviews have bemoaned the low levels of evidence for many treatments which have been tried in an attempt to alleviate pain associated with SCI.[9,10] To the authors' knowledge, no studies have examined antidepressants adjuvant to gabapentin or pregabalin. This project endeavored to characterize pain relief related to SCI from a real-world medical practice.

Longitudinally, individuals who were prescribed single medication therapy, as opposed to combination therapy, during their inpatient rehabilitation reported higher levels of pain following awakening 6 months later. At 6-month follow-up, treatment group was not associated with pain ratings over the past week, past 24 hours or at the time of assessment; however, maintaining the same therapy established in inpatient rehabilitation was associated with lower reported levels of pain over the past 24 hours and 30 minutes after awakening compared to individuals who did not maintain the same therapy. It may be that the medication therapy was not alleviating the subject's pain and they needed to abandon that course of treatment with no alternative.[27] Though we have no evidence to support this, it stands to reason that people probably will not be willing to pay for a medication which they feel does not provide them any relief and may come with additional side effects. It is also possible that subjects who maintained therapy were more adherent and because of this "healthy-user effect", they experienced lower levels of pain or, because of good medical adherence generally, also had better skills with which to cope with their pain on a daily basis. Previous studies have indicated that patients who adhere to their prescribed medication regime (even in cases of placebo) tend to experience better health overall.[28,29]

At baseline, individuals on neither therapy reported lower pain ratings than individuals on both or only one therapy of interest. This may be an artifact of pain maintenance with the medical team responding to individuals who report higher ratings of pain by prescribing more medication. At 6-month follow-up, higher reported cross-sectional measures of pain were related to higher scores on a depression questionnaire. This finding is not surprising given that pain is often related to depression and vice versa.[14,30]

Direct and simple comparison of our findings to those of others is inappropriate due to a lack of data from prior reports. Few studies have even been conducted on neuropathic pain management in acute SCI and most treatments are derived from what has worked for other neuropathies.[6,8,9]

This is a very small observational study and findings from it should be interpreted with caution due to concerns of residual confounding. First, the sample was drawn from one clinic and one prescribing physician. The treatment pattern from this group may differ from a national sample. There may be additional factors that were not measured which could account for pain management. The methods of classifying treatment group may have also increased the risk of residual confounding. It is unknown what other methods subjects may have used for controlling their pain beyond medication (i.e. meditation, activities to keep their mind off of the pain, massage, physical therapy, acupuncture, self-medication with over the counter or illicit substances, alcohol use, etc.).[27,31–34] Some studies have indicated that nonpharmacological strategies are as important or maybe even more so at controlling pain.[11] There may be a relationship between the types of pain the subject experiences and how well medication can manage that pain. Additionally, this study examined multiple models for the various pain rating time points (previous week, previous 24 hours, 30 minutes upon awakening and at the time of assessment) which may have increased the chance of finding a false positive. Further analysis is needed to discern these and other factors that may be associated with management of pain in those with a traumatic SCI.

The study had several notable strengths. The groups analyzed in this study did not significantly differ on key demographic variables and are roughly comparable to the general population of newly sustained SCI injuries.[35] This study was able to follow several individuals for many months in a population that is known to be difficult to follow-up. The pain ratings obtained were very detailed and provide additional information about multiple types of SCI-associated pain that has not always been well characterized in the past. The study compared patients initiating various treatments for pain control and this "new user" design ensures the accurate capture of baseline demographics and early events.

The findings in this small study underscore what we already know about pain in SCI as well as what we still do not know. Pain is a significant part of life after SCI. It can interfere with activities of daily living, social interactions and relationships, sleep, and quickly drive up the cost of healthcare for an individual.[11,34,36] Pain in SCI and possible effective treatments are very important areas of research. Available treatments for SCI-related NP are imperfect and may not consistently provide full relief; however, it appears that maintaining therapy may be related with reduced levels of pain in subjects with SCI. Further research is needed to elucidate factors related to pain intensity as well as pain management.

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